

REMARKS

A. Status of the Claims

Claims 1-73 were pending at the time of the Action. Claims 20-25, 30-32, 34, 35, 40, 41, 67, and 70-73 were previously withdrawn. Claims 1, 18, 26, 36, and 66-69 have been amended. Support for these amendments is found throughout the specification and the original claims, for example in the specification at page 5, lines 9-13. No claims have been added or cancelled. Therefore, claims 1-19, 26-29, 33, 36-39, 42-66, 68 and 69 are pending and presented herein for reconsideration.

B. Rejections Under 35 U.S.C. § 112

The Examiner alleges that the claims are indefinite. In particular the Examiner objects to the recitation "wherein said . . . particles . . . are retained on said first . . . medium" as allegedly indefinite. Although Applicants respectfully disagree, the claims have been amended to expedite prosecution.

Claim 1 currently recites "whereby adenovirus particles . . . are retained on said first chromatographic medium with a retention rate of about 10^{11} adenovirus particles or more per ml resin; (b) eluting adenovirus particles from said first chromatographic medium . . . (c) . . . wherein said second chromatographic medium . . . retains about 10^9 adenovirus particles or less per ml resin . . ." Thus, the claims now specify the rate at which the particles are retained on the first chromatographic medium. The remaining independent claims have been amended in a similar manner.

A proper evaluation of claim language under the second paragraph of 35 U.S.C. § 112 requires that the claim be read in light of the specification as interpreted by one of ordinary skill in the art. *North Am. Vaccine, Inc. v. American Cyanamid Co.*, 7 F.3d 1571, 1579, 28 USPQ 2d 1333, 1339 (Fed. Cir. 1993); *In re Moore*, 439 F.2d 1232, 1235 (C.C.P.A. 1971). The

specification describes the currently claimed methods as using “bound mode” and “flow mode” chromatography. *See* Specification at page 4, line 19 – page 5, line 13. “Bound mode is taught as a technique where the adenovirus particles are retained on the chromatographic medium at a retention rate of about 10^{11} adenovirus particles per ml resin and the contaminants remain suspended in the mobile phase. *Id.* “Flow mode” is taught as a technique where the contaminants are specifically retained on the chromatographic media and the adenovirus particles pass through in the mobile phase. *Id.* When the chromatographic medium in performing in flow mode, the retention rate of the adenovirus is about 10^9 adenovirus particles or less per ml resin. *Id.* A person having skill in the art would recognize that in step (a), the adenovirus particles are retained on the chromatographic medium in bound mode until eluted in step (b). Similarly, a person having skill in the art would recognize that the adenovirus particles flow through the second chromatographic medium in step (c). Thus, in light of the teachings of the specification and the knowledge of a person skilled in the art, the claims are definite.

Further, a person having ordinary skill in the art would recognize the conditions that are required for the particle to elute and have the ability to manipulate those conditions as appropriate. *See, e.g.,* Specification at page 4, lines 7-18. Use of a well known term of art in the specification without detailed definitions thereof does not render claims utilizing that same language indefinite. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556-58, 220 USPQ 303, 315-16 (Fed. Cir. 1983). As the claim language would be readily understood to a person having skill in the art, it is definite.

The Examiner further objects to the repeating use of the term “said eluate” in claim 1, which would allegedly render the claim indefinite. Although Applicant respectfully believes that the claim is definite, the claims have been amended to expedite prosecution. In particular, the

claims have been amended to refer to the “first” and “second” eluate or eluant, as appropriate. Each of these are introduced earlier in the claim, and no other eluates are recited. Therefore, a person having skill in the art would recognize which eluate is being referred to in each step.

For at least the above reasons, the claims are definite. Withdrawal of the rejections is respectfully requested.

C. Rejections Under 35 U.S.C. § 103

All claims stand rejected under 35 USC 103(a) for allegedly being obvious over Shabram *et al.* in view of Boyer *et al.* Applicant respectfully traverses.

It is well settled that “[t]he examiner bears the initial burden of factually supporting any *prima facie* case of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness.” MPEP § 2142. Here, no *prima facie* case of obviousness has been established.

In making a determination as to whether a *prima facie* case of obviousness exists, the examiner should: (A) determine the “scope and content of the prior art;” (B) ascertain the “differences between the prior art and the claims at issue;” (C) determine “the level of ordinary skill in the pertinent art;” and (D) evaluate evidence of secondary considerations. *Graham v. John Deere*, 383 U.S. 1, 17, (1966); *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007); *see also* MPEP § 2141. Furthermore, the following tenets of patent law must be adhered to: (A) the claimed invention must be considered as a whole; (B) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (D) reasonable expectation of success is the standard with which obviousness is determined. MPEP § 2141(II).

1. The Currently Pending Claims

The currently pending claims all require a two step process for preparing adenovirus particles. In the first embodiment, one step involves a chromatography medium where the adenovirus particles are retained on the chromatographic medium with a retention rate of about 10^{11} or more adenovirus particles per ml resin, *i.e.*, are in the bound mode until eluted, and the other step involves a chromatography medium where the adenovirus particles are retained on the chromatographic medium with a retention rate of about 10^9 or less adenovirus particles per ml resin, *i.e.*, are in flow mode through the chromatographic medium. In the second embodiment, in both steps the adenovirus particles are retained on the chromatographic medium with a retention rate of about 10^9 or less adenovirus particles per ml resin, *i.e.*, are in flow mode through the chromatographic medium. In some claims, anion exchange medium is used in the bound mode and dye affinity material is used in the flow through mode.

2. The Scope and Content of the Prior Art

Shabram teaches a three step method for purifying viral vectors. This method involves “enzymatically treating the cell lysate comprising the viral vector containing the therapeutic gene; chromatographing the enzymatically treated cell lysate on a first resin; and chromatographing the eluate from the first column on a second resin.” Shabram at col. 2, lines 15-20. In the method disclosed in Shabram, the adenovirus particles in Shabram **are bound** to the second chromatographic medium and only subsequently eluted therefrom by a different solvent. Thus, the disclosed method involves the use of bound mode chromatography in both steps. As acknowledged in the Action, Shabram also teaches the use of chromatographic methods that use metal affinity and hydrophobic interaction, but does not teach a method that uses dye affinity chromatography.

Boyle is cited as teaching that a DEAE – blue affinity dye protocol has been used to purify other proteinaceous materials from a complex biological mixture. Boyer teaches purification of a completely different product, namely a specific protein, Alkaline Protease (AP). Boyer, col. 2, lines 8-10. Further, Boyer teaches a purification method where the protein is not bound by DEAE cellulose but rather is in the eluant, which is subsequently applied to agarose with blue dye affinity ligand, to which the protein is bound. Boyer, col. 11, lines 52-67.

3. The Differences Between the Prior Art and the Current Claims Are Not Obvious

None of the cited references, alone or in combination, teach a method of purifying adenovirus particles that include a step where an adenovirus particle is bound to the chromatographic medium and a second step where an adenovirus particle flows through the chromatographic medium. Shabram teaches a method that uses a first chromatographic medium that binds the viral vector and then a second chromatographic medium that also binds the viral vector to further purify the virus preparation. Boyle does not remedy the deficiency of Shabram. Importantly, Boyer teaches a method for purifying a specific protein, not an adenovirus. Boyer, col. 2, lines 8-10. The failure of an asserted combination to teach or suggest each and every feature of a claim remains fatal to an obviousness rejection under 35 U.S.C. § 103. *See In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974) (emphasis added) (to establish *prima facie* obviousness of a claimed invention, all the claim features must be taught or suggested by the prior art); MPEP § 2143.03. As the Supreme Court stated in *KSR Int'l v. Teleflex Inc.*, “there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). Thus, it remains well-settled law that obviousness requires at least a suggestion of all of the features in a claim. *See In re Wada and Murphy*, citing

CFMT, Inc. v. Yieldup Intern. Corp., 349 F.3d 1333, 1342 (Fed. Cir. 2003) and *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). Shabram teaches a purification method where the adenovirus particles are bound to the chromatographic medium in both steps, and Boyer does not teach a method of purifying adenovirus particles at all. Therefore, neither references teaches or suggests a method that includes a step where the adenovirus particle flows through the chromatographic medium, and the current claims are not obvious in light of the cited references.

Further, a person having skill in the art would have no reasonable expectation of success in using a combined chromatography method as currently claimed. Rather, in light of the teachings of Shabram that successful purification of an adenovirus particle involves two chromatography steps in which the chromatographic medium retains the viral particle in bound mode, a person having skill in the art would believe that a method where the chromatographic medium does not retain the viral particle, *i.e.*, includes a flow mode step, in at least one step would not be successful. If anything, a person of ordinary skill in the art would be led down a path divergent from the currently claimed method involving a chromatographic medium that does not retain the adenovirus particles, *i.e.*, it teaches away from the use of flow mode method. A “reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the Appellant.” *Tec Air Inc. v. Denso Mfg. Michigan Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999). The fact that Shabram actually teaches away from the currently claimed invention is a strong indicator of non-obviousness.

Furthermore, a person having skill in the art would not refer to Boyer to determine appropriate methods for purifying adenovirus particles. Boyer relates to purification of a completely different product, namely a specific protein, Alkaline Protease (AP). This protein is

not the same as an adenovirus and, as the skilled person is well aware of, purification of any molecule depends heavily on the individual properties of such molecule so that any teaching of purification of an unrelated molecule cannot simply be extrapolated. As specifically taught in Shabram, purification of an adenovirus poses additional difficulties. *See* Shabram, col. 1, line 34 – col. 2 line 7. Thus, the skilled person reading Shabram would not easily depart from the teaching therein and apply completely different columns in the first place. Certainly, the skilled person would not have a reasonable expectation of success for purifying adenovirus from teachings relating to the purification of a specific AP protein in Boyer. Furthermore, Boyer teaches that the protein is not bound by DEAE cellulose but rather is in the eluant, which is subsequently applied to agarose with blue dye affinity ligand, to which the protein is bound. This is in complete contrast to the purification method as currently claimed, where the adenovirus particles bind to the anion exchange material and flow through the dye affinity material. As such, Boyer also teaches away from the currently claimed method.

In contrast to the assertion in the Action that the use of serial chromatographic techniques is “notoriously old and well known in the art of protein or virus or even adenovirus purification,” Applicants note that a person having skill in the art would recognize that the purification of biological materials is a highly unpredictable art and finding a suitable process for a given biological material requires significant investments and significant efforts from teams of innovative and highly trained skilled persons. This is actually emphasized by the teachings of Shabram, which indicated that the discovery of the disclosed purification process was “unexpected and surprising.” Shabram at col. 2, lines 12-20. In fact, a person having skill in the art would recognize that: (i) there exist huge differences between proteins and viruses, (ii) there exist huge differences between different viruses, and (iii) there exist huge differences in modes

of operation, conditions, *etc.* that are suitable for each individual protein or virus, and that none of these variables can be predicted with any certainty, so that for a specific purification process, as currently claimed, there can never be a reasonable expectation of success based on purification processes described in the art for entirely different entities. Therefore, a person having skill in the art would have no reasonable expectation of success in using a combined chromatography method as currently claimed.

Furthermore, it is important “to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements” in the manner claimed. *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007). In particular, the Court noted that there should be an “explicit” analysis regarding “whether there was an **apparent reason** to combine the known elements **in the fashion claimed** by the patent at issue.” *Id.* at 417 (emphasis added). As discussed above and unlike in *KSR*, here there is no predictable variation of previously known methods and the techniques of the prior art are not at all used in the same way in the currently claimed method. Thus, a person of ordinary skill in the art would not have had an apparent reason to combine the teachings of Shabram and Boyer as asserted.

Further, in contrast to the assertions in the Action, dye affinity chromatography is not closely analogous to chromatographic techniques that rely on metal affinity or hydrophobic interaction. The only relation between these techniques appears to be that they are chromatographic techniques, which for reasons outlined above does not make them related. As a matter of fact, these techniques use completely different principles for separation of molecules and would not be viewed by the skilled person as closely analogous to each other. Therefore, a person skilled in the art would not view the methods as interchangeable and, as such, would have had no apparent reason to modify the method of Shabram as suggested in the Action. It appears

that the Examiner is relying on hindsight to find a motivation to combine these references. The use of hindsight, however, is not appropriate. See *W.L. Gore Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983); MPEP § 2143.01. In fact, KSR explicitly warns against the pitfall of an *ex post facto* analysis.

Applicant is thus of the view that the Examiner has not met his burden to provide a *prima facie* case of obviousness. With respect to the dependent claims, if an independent claim is nonobvious under 35 U.S.C. § 103(a), then any claim depending therefrom is nonobvious. MPEP § 2143.03. Therefore, the above arguments apply equally to the rejected dependent claims. Applicant respectfully submits that the specifically claimed processes are not obvious in view of the art.

For at least these reasons, the rejection should be withdrawn.

D. Conclusion

Applicant believes that the foregoing is a complete response to the February 3, 2010 Office Action. The Examiner is invited to contact the undersigned attorney at (512) 536-3123 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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Date: May 11, 2010